Integra.
Dermal Regeneration Template

INTEGRA Dermal Regeneration Template

DESCRIPTION

INTEGRA Dermal Regeneration Template is a bilayer membrane system for skin replacement. The dermal replacement layer is made of a porous matrix of fibers of cross-linked bovine tendon collagen and glycosaminoglycan (chondroitin-6-sulfate) that is manufactured with a controlled porosity and defined degradation rate. The epidermal substitute layer is made of a thin polysiloxane (silicone) layer to control moisture loss from the wound.

INTEGRA Dermal Regeneration Template is aseptically processed. The inner foil pouch and product should be handled using sterile technique. INTEGRA Dermal Regeneration Template should not be sterilized, as this would alter the intrinsic properties of the product.

INDICATIONS

INTEGRA Dermal Regeneration Template is indicated for the postexcisional treatment of life-threatening full-thickness or deep partial-thickness thermal injuries where sufficient autograft is not available at the time of excision or not desirable due to the physiological condition of the patient.

INTEGRA template is also indicated for the repair of scar contractures when other therapies have failed or when donor sites for repair are not sufficient or desirable due to the physiological condition of the patient.

CONTRAINDICATIONS

Use of INTEGRA Dermal Regeneration Template (INTEGRA template) is contraindicated in patients with known hypersensitivity to bovine collagen or chondroitin materials.

INTEGRA template should not be used on clinically diagnosed infected wounds.

WARNINGS

Excision of the wound must be performed thoroughly to remove all coagulation eschar and nonviable tissue. INTEGRA template will not "take" to nonviable tissue. Leaving any remaining nonviable tissue may create an environment for bacterial growth.

Hemostasis must be achieved prior to applying INTEGRA template. Inadequate control of bleeding will interfere with the incorporation of INTEGRA template.

PRECAUTIONS

There have been no clinical studies evaluating INTEGRA template in pregnant women. Caution should be exercised before using INTEGRA template in pregnant women. Such use should occur only when the anticipated benefit clearly outweighs the risk.

In clinical trials, the use of INTEGRA template was evaluated in a small number of patients with chemical, radiation, or electrical burns. A surgeon's decision to use INTEGRA template on these wounds should be based on their evaluation of the wound and its suitability to excisional therapy, the likelihood that a viable wound bed will be created by excision, and whether the possible benefit outweighs the risk in this patient population.

INTEGRA template should be applied on the day of excision. Delaying the application of INTEGRA template may substantially impair the take of the material.

Appropriate techniques to minimize pressure and shearing should be used to reduce risk of mechanical dislodgement.

Placing the patient in hydrotherapy immersion may interfere with proper incorporation of the INTEGRA template and cause premature separation of the silicone layer and nonadherence of the template. Caution must be employed to not remove the newly formed neodermal tissue when removing the silicone layer. INTEGRA template must NOT be excised off the wound.

The extent of scarring associated with the use of this product has not been determined.

ADVERSE EVENTS

Burn Patients

INTEGRA template has been found to be well tolerated in 4 prospective clinical trials involving 444 burn patients. There were no reports of clinically significant immunological or histological responses to the implantation of INTEGRA template. There were no reports of rejection of INTEGRA template.

Adverse events in the postapproval study were similar to those observed in the previous clinical trials and are common in populations of critically ill burn patients regardless of type of treatment used. There were no trends noted. There were 6 adverse events which were rated by the investigator as being related. These events were all single occurrences except for sepsis (2). These adverse events occurred in less than 1% of the safety population.

Incidence of adverse events occurring in ≥1% of the safety population in the Postapproval Study are as follows:

Adverse Events	n/N (%)
Sepsis	50/216 (23.1%)
Death	30/216 (13.9%)
Infection	6/216 (2.8%)
Thrombophlebitis	6/216 (2.8%)
Kidney Failure	6/216 (2.8%)
Necrosis	5/216 (2.3%)
Hemorrhage	5/216 (2.3%)
Heart Arrest	4/216 (1.9%)
Apnea	4/216 (1.9%)
Pneumonia	4/216 (1.9%)
Allergic Reaction	3/216 (1.4%)
Fever	3/216 (1.4%)
Multisystem Failure	3/216 (1.4%)
Atrial Fibrillation	3/216 (1.4%)
Gastrointestinal Hemorrhage	3/216 (1.4%)
Kidney Abnormal Function	3/216 (1.4%)

Adverse events reported in less than 1% of the population were as follows: enlarged abdomen, accidental injury, hypothermia, peritonitis, hypotension, peripheral vascular disorder, arrhythmia, cardiomyopathy, cardiovascular disorder, congestive heart failure, pulmonary embolism, dyspnea, aspiration pneumonia, hypoxia, pleural effusion, respiratory distress syndrome, cholecystitis, gastrointestinal perforation, hepatorenal syndrome, intestinal obstruction, and pancreatitis.

Adverse events reported in the previous studies are as follows:

Coded Symptom	Multicenter N=149 (% frequency)	Anatomic Site N=59 (% frequency)	Meshedvs Sheet N=20 (% frequency)
Death	37(24.8%)	19 (32.2%)	3 (15%)
Sepsis	17 (11.4%)	4 (6.8%)	1 (5.0%)
Apnea	13 (8.7%)	5 (8.5%)	0 (0.0%)
Pneumonia	10 (6.7%)	0 (0.0%)	0 (0.0%)
Heart Arrest	7 (4.7%)	6 (10.2%)	0 (0.0%)
Kidney Failure	5 (3.4%)	4 (6.8%)	0 (0.0%)
Respiratory Distress	3 (2.0%)	0 (0.0%)	0 (0.0%)
Infection	2 (1.3%)	0 (0.0%)	0 (0.0%)
Lung Disease	2 (1.3%)	0 (0.0%)	0 (0.0%)
Dyspnea	1 (0.7%)	1 (1.7%)	0 (0.0%)
Adrenal Insufficiency	1 (0.7%)	0 (0.0%)	0 (0.0%)
Agitation	1 (0.7%)	0 (0.0%)	0 (0.0%)
Convulsion	1 (0.7%)	0 (0.0%)	0 (0.0%)
Hematemesis	1 (0.7%)	0 (0.0%)	0 (0.0%)
Hemoptysis	1 (0.7%)	0 (0.0%)	0 (0.0%)
Liver Cirrhosis	1 (0.7%)	0 (0.0%)	0 (0.0%)
Nonadherence	1 (0.7%)	0 (0.0%)	0 (0.0%)
Shock	1 (0.7%)	0 (0.0%)	0 (0.0%)
Skin Discoloration	1 (0.7%)	0 (0.0%)	0 (0.0%)
Asystole	0 (0.0%)	0 (0.0%)	1 (5.0%)
Cerebral Artery Infarct	0 (0.0%)	1 (1.7%)	0 (0.0%)
Metastatic Ovarian Cancer	0 (0.0%)	1 (1.7%)	0 (0.0%)
Peritonitis	0 (0.0%)	1 (1.7%)	0 (0.0%)
Sarcoidosis	0 (0.0%)	0 (0.0%)	1 (5.0%)
Third Degree Burn	0 (0.0%)	1 (1.7%)	0 (0.0%)
Multisystem Failure	0 (0.0%)	3 (5.1%)	0 (0.0%)

With the exceptions of wound fluid accumulation, positive wound cultures and clinical wound infection, none were directly related to the use of INTEGRA template.

In these clinical trials, data were collected regarding wound infection. The consequences of infection at sites treated with INTEGRA template included partial or complete loss of take (incorporation into the wound bed) of INTEGRA template. Infection rates in sites treated with INTEGRA template in the three clinical trials supporting the PMA ranged from 14 to 55%. The overall infection rate for the Postapproval Study was 16.3%.

Contracture Reconstruction Patients

The following adverse events were reported in a Reconstructive Surgery Study involving 20 patients with 30 anatomical sites and a Retrospective Reconstruction Contracture Survey involving 89 patients and 127 anatomic sites.

Incidence of Adverse Events in the Reconstructive Contracture Surgery Study and Retrospective Contracture Reconstruction Survey

	Reconstructive Surgery Study N=30 Sites	Retrospective Contracture Reconstruction Survey N= 127 sites
Adverse event	n/N (%)	n/N (%)
Infection	0/30 (0.0%)	26/127 (20.5%)
Fluid under Silicone Layer	0/30 (0.0%)	18/127 (14.2%)
Partial graft loss (INTEGRA)	0/30 (0.0%)	2/127 (1.6%)
Failure to take (INTEGRA)	0/30 (0.0%)	8/127 (6.3%)
Shearing/Mechanical shift (loss of INTEGRA)	1/30 (3.3%)	6/127 (4.7%)
Hematoma	5/30 (16.7%)	3/127 (2.3%)
Granulation tissue formation	0/30 (0.0%)	4/127 (3.1%)
Delayed Healing	0/30 (0.0%)	1/127 (0.8%)
Separation of the Silicone Layer	0/30 (0.0%)	1/127 (0.8%)
Seroma	0/30 (0.0%)	1/127 (0.8%)
Pruritis	0/30 (0.0%)	1/127 (0.8%)
Epidermal autograft loss >15%	2/30 (6.7%)	7/127 (5.5%)
Epidermal autograft loss <15%	7/30 (23.3)	9/127 (7.1%)

There were no infections reported in the Reconstructive Surgery Study and the reported infection rate was 20.5% in the Retrospective Contracture Reconstruction Survey. No deaths were reported.

SUMMARY OF CLINICAL STUDIES

Burn Patients

INTEGRA template has been evaluated in over 1,200 wound sites in 444 burn patients evaluated in a series of 4 studies:

- Multicenter Safety and Efficacy Clinical Trial (Pivotal)
- Anatomic Site Study
- Meshed vs. Sheet INTEGRA template Study
- Postapproval Study

Demographic, safety and effectiveness data for INTEGRA template are summarized in the table below.

Data Across Studies

Variable		Multicenter Study	Anatomical Site Study	Meshed vs. Sheet Study	Postapproval Study
Year		**1983-1989**	**1985-1992**	**1989-1992**	**1997-2000**
Number of Patients		149	59	20	216
Number of Wound Sites		207	130	59	841
Age:	(Mean ± SD)	32.0 ± 21.5	49.2 ± 21.2	30.1 ± 15.6	34.7 ± 23.9
	Range	<1 – 88Y	19 – 93Y	4 – 59Y	4M – 87Y
Gender:	Male	112 (75.2%)	33 (55.9%)	16 (80%)	151 (69.9)%
	Female	37 (24.8%)	26 (44.1%)	4 (20%)	65 (30.1%)
Race:	Caucasian	98 (65.8%)	56 (94.9%)	14 (70.0%)	151 (69.9%)
	Black	32 (21.5%)	0 (0.00%)	6 (30.0%)	38 (17.6%)
	Hispanic	15 (10.1%)	3 (5.1%)	0 (0.00%)	20 (9.2%)
	American Indian	3 (2.0%)	0 (0.00%)	0 (0.00%)	1 (0.5%)
	Asian	1 (0.7%)	0 (0.00%)	0 (0.00%)	4 (1.8%)
	Other	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.9%)
% BSA Total Burn:	(Mean ± SD)	45.7 ± 18.6	49.8 ± 24.6	53.6 ± 19.4	36.5 ± 24.7
	Range	14.5 – 88.5	1 – 97	30 – 90	<1– 95
% BSA Full-Thickness:	(Mean ± SD)	31.8 ± 20.8	42.5 ± 24.0	35.4 ± 22.4	27.9 ± 24.4
	Range	0 – 88.5	1 – 95	0 - 78	0 – 95
% Inhalation Injury		42%	62.5%	50%	45%
Mean Take		65.1%*	77.6%	80.6%	76.2%
Median Take		80%*	95%	100%	98%
Infection		55%	14%	25%	16.3%
Mortality		24.8%	32%	15%	13.9%

** Paired comparative wound sites.*

Multicenter Safety and Efficacy Clinical Trial (Pivotal Study)

In the pivotal multicenter clinical trial, 149 patients were evaluated for safety and 106 patients (with 136 comparative wound sites) were included in an assessment of efficacy. The demographic profile was: mean age 32.0, age range <1 to 88 years, gender: 112 males and 37 females and a mean %TBSA burn of 45.7% with a range of 14.5%–88.5%. Take, which was defined as the median fractional area of the wound site to support epidermal growth, was the main efficacy variable and was bimodally distributed. In the multicenter trial, INTEGRA template had successful take (take >10%) in 69% of the wound sites (94 of 136). For this group of wound sites with successful take, the mean take was 81%, and the median take was 90%. Over 80% of the wound sites in this successful take group had greater than 60% take. INTEGRA template failed to take (take ≤10%) in 31% of the wound sites (42 of 136 comparative wound sites). For this group, the mean take was 1.7% and the median take was 0%.

The INTEGRA template neodermis provided a viable surface for the successful transplantation of thin, meshed and spread epidermal autograft. The take of epidermal autograft was bimodally distributed. In the multicenter trial, epidermal autograft had successful take (take >10%) in 90.5% of the sites (95 of 105 comparative wound sites). For this group of wound sites with successful take, the mean was 84% and the median take was 90%. Over 80% of the wound sites in this successful take group had greater than 65% take. Epidermal autograft failed to take (take <10%) in 9.5% of the sites (10 of 105 comparative wound sites). For this group, the mean take was 1.7% take and the median take was 0%.

No significant difference was seen between the total time for burn healing for wounds treated with INTEGRA template and for wounds treated with temporary wound covers. The healing time of thin epidermal autograft on the INTEGRA template neodermis was comparable to that of conventional autograft. Donor sites for thin epidermal autograft healed faster and allowed for more cycles of reharvesting than conventional donor sites.

Histological Evaluation

Three hundred thirty-six serial biopsies were obtained from 131 patients participating in the multicenter clinical trial ranging from 7 days to 2 years after application of INTEGRA template. A histological study of the wound healing in the burned areas was conducted. An intact dermis was achieved with regrowth of apparently normal reticular and papillary dermis. No scar formation appeared in the biopsies of patients examined.

Anatomic Site Study

In the noncomparative single-center anatomic site study, 59 patients (130 wound sites) were evaluated for safety and 41 patients (104 wound sites) were evaluated for efficacy parameters. The demographic profile was: mean age, 49.2, age range 19-93 years, gender: 33 males and 26 females and a mean %TBSA burn of 49.8% with a range of 1%-97%. The mean take of INTEGRA template was 77.6%, and the median take was 95%. The mean take of the epidermal autograft was 77.8% and the median take was 85%. Median take was similar for the various anatomic locations evaluated. However, the small number of patients and noncomparative nature of the study prevented conclusions from being made.

Meshed vs. Sheet Study

A pilot study was conducted on 20 patients (59 wound sites) to compare 2:1 meshed (but not expanded) and sheet INTEGRA template. The demographic profile was: mean age, 30.1, age range 4-59 years, gender: 16 males and 4 females and a mean TBSA of 53.6% with a range of 30-90%. The mean take of INTEGRA template in this study was 80.6% and the median take was 100%, while the mean take for the epidermal autograft was 86.5% and the median take was 95%. However, due to the small number of patients and study design, statistical conclusions could not be drawn.

Postapproval Study

A Postapproval Study of INTEGRA template evaluated the safety and effectiveness in 216 patients, 841 wound sites. There were 222 patients enrolled in the study, however 6 patients did not meet entry criteria (3 did not sign the patient informed consent form, 3 did not receive INTEGRA template) resulting in

216 patients entered into the study. The demographic profile was: mean age 34.7, age range 4 months to 87 years, gender: 151 males and 65 females and a mean %TBSA burn of 36.5% with a range of <1% to 95%. Effectiveness was measured by graft take. Overall mean percent take for INTEGRA template was 76.2% and the median percent take for INTEGRA template was 98%. The mean take of epidermal autograft was 87.4% with median take of 95%. The rate of infection in the study patients was 16.3% (13.2% superficial and 3.1% invasive). Patient mortality was 13.9%. Data analysis indicated that mortality was related to patient age, percent total body surface area burned, presence of inhalation injury, and presence of infection at a non-INTEGRA template treated wound site. Invasive infection at an INTEGRA template wound site was not a significant risk factor for mortality.

SUMMARY OF CLINICAL STUDIES

Contracture Reconstruction Patients

Reconstructive Surgery Study

This study evaluated the clinical and histologic outcomes in 20 consecutive patients (30 anatomic sites) whose scars and contractures were treated with INTEGRA template. Patients' mean age was 27.6 years, with an age range of 4-54 years. Patient follow-up ranged from 3 to 24 months. The mean take was derived from the adverse event data and was calculated to be 94.2% for INTEGRA template and 86.3% for epidermal autograft. Efficacy was evaluated using the Vancouver Burn Scar Assessment scale by an independent review panel, a visual analog scale of patient satisfaction and histological evaluations of patient biopsies. The Vancouver Burn Scar Assessment scale ranges from 0 (normal) to 15. The mean preoperative Vancouver Burn Scar Assessment was 13.3 and the mean postoperative score was 9.0. For the patient satisfaction assessments, patients or their parents completed a questionnaire at least 3 months after the second stage of the reconstruction. A visual analog scale was used in which a score of 0%=preoperative scar and a score of 100%=normal skin with no scar. Patients/parents reported mean scores of 72% for range of movement, 62% for softness, 59% for appearance, 27% for pruritis and 14% for dryness.

Retrospective Contracture Reconstruction Survey

This survey requested information from physicians already using INTEGRA template on the use of the product for contracture reconstruction. Information was received from 13 of 19 physicians surveyed who reported on 89 patients and 127 anatomic sites. The demographic profile for the reported patients were: mean age 24.8, age range <1 to 72, gender 52 males and 37 females. The adverse events of this survey are provided in tabular form in the adverse event section.

INFORMATION FOR USE

INTEGRA template facilitates the formation of a neodermis by the body. The collagen dermal portion serves as a template for the infiltration of fibroblasts, macrophages, lymphocytes, and capillary endothelial cells which form the neovascular network. As healing progresses, the collagen-GAG layer is resorbed and new collagen is deposited by the fibroblasts to form the neodermis. Upon adequate vascularization of the neodermis and the availability of the donor autograft, the silicone layer is removed and a thin, meshed layer of epidermal autograft is placed over the neodermis. Cells from the epidermal autograft grow and form a mature epidermis thereby closing the wound, and resulting in a functional dermis and epidermis.

Patient Evaluation and Selection of Sites for Application of INTEGRA Template

As the extent of the patient's thermal injury is evaluated, all burn areas requiring prompt excision and grafting should be identified. INTEGRA template may be applied to all excised wound sites.

SURGICAL APPLICATION

Scheduling Surgery for INTEGRA Template Application

INTEGRA template must be applied to a viable wound bed following surgical excision of burn wounds. Surgery may be scheduled as soon as the patient is stabilized. Surgery should be staged as appropriate.

Perioperative Antibiotics

Perioperative antibiotics are recommended to be administered according to the clinical judgment of the practitioner

Opening the package